**ABSTRACT**

Background/Purpose: Interleukin-1 receptor-associated kinase 4 (IRAK4) is a key mediator of the innate immune response through its role in several NF-κB signaling pathways. These pathways are involved in critical cellular processes such as the induction of unstable (high-energy) hydration and Toll-like receptors (TLRs). IRAK4 activation is mediated by MYD88, a common signaling adaptor protein downstream of TLRs, and Toll receptor (TIR) family members that mediate a broad range of immune responses to PAMPs (pathogen-associated molecular patterns) and DAMPs (damage-associated molecular patterns).

Methods: Using this innovative structure-based approach, we designed, synthesized and tested small molecule inhibitors of IRAK4. The compounds were evaluated for impact on LPS-, IL-1-, R848-, and/or CpG-mediated cytokine production in human peripheral blood mononuclear cells (PBMCs) and whole blood. IRAK4 inhibitors were evaluated in vivo in acute LPS challenge, chronic collagen-induced arthritis (CIA), imiquimod-induced psoriasis and MSU air pouch gout models.

Results: We feature three highly potent, selective IRAK4 inhibitors, ND-2110, ND-2158 and ND-2110, which are 100-fold selective for IRAK4 over IKKα, IKKβ, IRAK1 and IRAK3. These compounds are highly effective against IRAK4 kinase activity, and reduced cytokine production in PBMCs in vitro and peripheral blood mononuclear cells (PBMCs) and whole blood.

Conclusions: Utilizing unique and innovative structure-based drug design, we have rapidly discovered potent and selective IRAK4 inhibitors as potential drug candidates for the treatment of autoimmune diseases.

**SUMMARY**

IRAK4 is a sought after target for the treatment of autoimmune diseases. Previous attempts to identify small molecule modulators of IRAK4 resulted in poor selectivity and inadequate drug-like properties. Using a physics-based computational approach, Nimbus has uncovered previously unexploited drivers of potency and selectivity. Nimbus compounds have good drug-like properties and are candidates for further development for treating inflammatory diseases.